Commentary on "Brain Environment Interactions: Stress, Posttraumatic Stress Disorder, and the Need for a Postmortem Brain Collection"

Toward a National PTSD Brain Bank

Matthew J. Friedman and William W. Harris

Scientific technology has brought us to new levels of understanding about the brain. Neuroimaging, animal, and behavioral studies have greatly increased our knowledge of the brain. Nevertheless, a great deal remains to be known. One exciting avenue for further research is the study of postmortem brain tissue. Brain banks have been established in multiple sites around the United States. They have been used to study depression, dementia, alcoholism and a wide variety of neurological disorders. We believe it is now time to establish a brain bank dedicated to Posttraumatic Stress Disorder (PTSD).

This commentary will argue that we should begin the process immediately to develop such a brain bank. First, we make the scientific argument regarding the necessity for establishing such a national resource. Next, we address key questions such as: what is a brain bank? How might it be managed? How will it carry out scientific research? And how will it adhere to the highest ethical criteria?

SCIENTIFIC RATIONALE

Epidemiological research on the aftermath of traumatic events has consistently reported two findings. First the vast majority of people exposed to terrorist attacks (Galea et al., 2002; Schuster et al., 2001) or natural disasters (Norris et al., 2002a; 2002b) report moderate to severe distress. Second, most people exposed to any traumatic event (e.g., rape, war, interpersonal violence, etc.) do not develop PTSD (Breslau et al., 1991; Kessler et al., 1995; Kulka et al., 1990). In other words, most acute posttraumatic reactions, no matter how severe, are transient. Only a minority persist as chronic psychiatric disorders. Among the general American population, lifetime PTSD prevalence is approximately 8% whereas it is much higher among populations at greater risk for exposure to trauma. For example, among Vietnam veterans who saw service in Southeast Asia, lifetime prevalence for PTSD was 30%.

Matthew J. Friedman, MD, PhD, is affiliated with the National Center for PTSD, US Department of Veterans Affairs, VA Medical Center, White River Junction, Vermont, and with the Departments of Psychiatry and Pharmacology, Dartmouth Medical School, Hanover, New Hampshire.

William W. Harris, PhD, is affiliated with the Children's Research and Education Institute, Belmont, Massachusetts.

This work was supported by the National Center for PTSD, U.S. Department of Veterans Affairs. The opinions expressed here are those of the authors, alone, and do not reflect official policy of either the Department of Defense or the Department of Veterans Affairs.

Address correspondence to Matthew J. Friedman, MD, National Center for PTSD, VA Medical Center (116D), 215 North Main Street, White River Junction, VT 05009. E-mail: Matthew.J.Friedman@Dartmouth.edu.

Current findings on risk and protective factors can only provide indirect clues regarding the difference between resilience and vulnerable individuals. Whether the focus is on genetic loading or social support, the scientific and clinical bottom line is to understand how various risk and protective factors affect the brain's capacity to process and cope with such highly charged emotional and potentially life-threatening events.

We have learned a great deal in recent years, thanks to enormous technological advances in brain imaging and genetic research. As detailed by Osuch and associates and Krystal and Duman (in this issue), functional brain imaging studies have confirmed in humans, the neurocircuitry of fear and anxiety inferred from animal research (Charney, 2004). In addition, hyper–reactivity of the amygdala and related structures, in conjunction with inadequate prefrontal cortical restraint, appears to be one abnormality associated with PTSD. Indeed, abnormalities in adrenergic sensitivity (Bremner et al., 1997) and benzodiazepine binding (Bremner et al., 2000) detected by functional brain imaging have begun to suggest neurobiological mechanisms and future targets for clinical intervention.

Genetic research in this area is not nearly so advanced. However, recent gene *x* environment interactions detected among depressed subjects have shown that (in contrast to homozygous or heterozygous carriers of the short allele) homozygotes for the long allele of the serotonin transporter gene are resilient in the face of adverse life experiences (Caspi et al., 2003). This suggests that similar findings may be detected among individuals with PTSD.

How abnormalities in cerebral blood flow, neuronal oxygen metabolism, brain ligand binding or variability in gene expression translate into vulnerability or resilience can only be clarified by a closer look. Osuch and colleagues mention many of the places where we need to look including: cytoarchitectonics, neurotransmitters and receptors, neuropeptides, enzyme synthesis, neurotropic factors, synaptic proteins, signal transduction pathways, markers of inflammation or infection, as well as neuronal regeneration and apoptosis. Perhaps we will find one or two key factors that predict vulnerability or resilience. More likely, several different multifactorial patterns will emerge regarding the interaction of several dynamic processes that predict an individual's ability or inability to cope with stressful and traumatic events.

Therefore, we agree with Osuch and associates and Krystal and Duman (in this issue) that we need a national PTSD brain bank through which postmortem tissue can be made available to investigate such fundamental questions. It is noteworthy that within the United States, there are currently 55 brain banks devoted to investigating schizophrenia, Alzheimer disease, alcoholism, mood and a variety of neurological disorders. A national facility is needed to promote our understanding of the impact on brain tissue of stress, trauma, adaptive (transient) posttraumatic reactions and chronic posttraumatic pathophysiology exemplified by PTSD. This is a challenge we can no longer ignore since, except for depression, the prevalence of PTSD is much greater than for all of these other disorders.

Furthering basic understanding of how traumatic experiences produce brain alterations and how such alterations mediate clinically significant abnormalities is especially pertinent to our nation's veterans and active duty military personnel. A total of 30% of all male and 25% of all female Vietnam war zone veterans experienced PTSD at some point after deployment to Southeast Asia. Among them, 15% and 8%, respectively, remained symptomatic 15 to 20 years after such exposure. In addition to significant psychiatric morbidity (Kulka et al., 1990), PTSD has also been associated with significant adverse medical consequences and associated costs (Boscarino, 1997; Schnurr & Green, 2004). Whether or not a higher or lower percentage of men and women deployed to Iraq and Afghanistan will exhibit PTSD, related disorders, or suicidal behavior, there is no question that a significant number of current military

personnel will be severely affected and incapacitated.

Although nonmilitary and nonveteran cohorts are at a lower risk in the American general population, more than half of all adult men and women will have been exposed to at least one traumatic event during their lives and eight percent will have developed PTSD (Kessler et al., 1995; Breslau et al., 1991). In nations at war or torn by internal strife, trauma exposure may affect 70 to 90% of the population and PTSD prevalence may reach 37% (De Jong et al., 2001).

Absence of PTSD is no guarantee that traumatized people have not been affected by such exposure. Indeed, there is evidence that successful coping with traumatic stress may still produce demonstrable biological abnormalities since adult female survivors of childhood sexual abuse without overt psychiatric disorder exhibited significant alterations in hypothalamic–pituitary–adrenocortical function (Heim et al., 2001). This observation is especially relevant to trauma–exposed but nonsymptomatic active duty personnel, veterans or civilian cohorts (such as policemen, firefighters, emergency medical technicians, humanitarian relief workers, etc.). Are there detectable alterations in brain function among people who have successfully coped with traumatic experiences? Do such alterations constitute a risk factor for subsequent behavioral, psychiatric or medical problems? Might the discovery of such abnormalities point the way to innovations in effective preventive and treatment strategies? These are some of the questions that could be addressed in a national brain bank.

OPERATING PRINCIPLES AND CONCERNS

We all stand a good chance of traumatic exposure during the course of our lives. Among those of us so exposed, approximately 20% will develop PTSD. PTSD is a common window, through which we can study the brain's response to a wide variety of environmental events that affect all components of our society—inner city and rural, military and civilian, child and adult, rich and poor, etc. (Ursano, personal communication Feb. 5, 2004). Therefore, we all are potentially vulnerable to the brain alterations caused by traumatic stress and PTSD. How would a brain bank, established to understand such alterations, operate?

A group of researchers from the Uniformed Services University of Health Sciences and the Department of Veterans Affairs (VA) National Center for PTSD have met regularly to consider this possibility. Although a detailed technical description of the collective vision for a national PTSD brain bank is beyond the scope of this brief commentary, it is useful to consider several key questions about this initiative.

WHAT IS A BRAIN BANK?

After death, there are many postmortem changes that affect the integrity of brain and other body tissues. As a result, any brains to be included in a brain bank must be processed, preserved, and stored according to strict histological criteria within a narrow window of time. Osuch and colleagues (this issue) have addressed many of the technical challenges regarding the establishment of an accurate diagnosis, tissue processing, preservation, and storage to insure that high quality, dependable material is available for research. Such tissue is then potentially available for investigations of cellular architecture, protein activity, gene expression, and other factors. The ultimate goal of such research is the discovery of better preventive and therapeutic strategies with which to combat the development of posttraumatic medical and psychiatric disorders.

Management of such a resource requires attention to five major activities: 1) establishment and enforcement of strict criteria for tissue processing and preservation; 2) development and oversight of assessment protocols to insure accurate antemortem or postmortem diagnostic evaluation; 3) a scientific peer review process by which research propos-

als from potential investigators are approved or disapproved; 4) a method for disseminating brain tissue to approved investigators; and 5) an executive committee that provides general oversight and coordination of these four activities, in addition to developing and monitoring strict protocols for the ethical acquisition and scientific use of brain tissue.

A brain bank devoted to traumatic stress and PTSD will have to address some unique challenges that set it apart from other brain banks. It is often possible to know, in advance, when (for example) an Alzheimer's or schizophrenia patient (or his or her family) has consented to donate a brain after death. Under such circumstances, adequate diagnostic assessment and preparations for tissue processing can be accomplished before death, thereby optimizing the quality of brain specimens and clinical information. In the case of sudden, unexpected traumatic death, however, successful tissue preparation can only be accomplished at specialized laboratories that have been established to address these problems. In addition, the quality of postmortem diagnostic assessment will depend on hospital records as well as retrospective information provided by key informants such as family members, loved ones, and friends.

Fortunately, there is a great deal of collective experience on which to draw, from the 55 brain banks devoted to other psychiatric and neurological disorders that are currently in operation. Some of these facilities have also mastered the complications posed by sudden unexpected death, especially in the case of suicide or automobile accidents.

WHO NEEDS A BRAIN BANK AND WHY?

We believe that a PTSD brain bank should be a national resource through which to understand brain alterations caused by PTSD. The primary goal is not just to develop better treatment but to identify preventive strategies. Using heart disease as a successful example, knowledge gained about metabolic and tissue abnormalities that increase the risk for heart disease, has generated a wide variety of successful preventive strategies, most notably the statin class of medications that lower cholesterol, triglycerides, and low density lipoproteins. Such a preventive approach is one public health goal of a brain bank, especially for people at risk for PTSD. Perhaps such research could lead to a "morning after pill" that could be given to recently traumatized children and adults in order to prevent the progression from an acute stress reaction to chronic PTSD. Therefore, given that over half of the U.S. population can expect exposure to at least one traumatic event during their lifetime, we assert that the nation, as a whole, needs a brain bank to foster normal recovery and prevent chronic PTSD among traumatized Americans. The highest area of concern for the brain bank must focus on children, active duty personnel, veterans, emergency responders, firefighters, police, and other individuals at risk.

HOW CAN WE IDENTIFY PTSD–SPECIFIC ABNORMALITIES?

This is a complicated question because 80% people with PTSD suffer from at least one other psychiatric disorder (Kessler et al., 1995). In general, there are already brain banks devoted to such comorbid disorders (e.g., depression, alcohol misuse, etc.) with which to compare the brains from PTSD patients. Furthermore, it appears likely that a number of brains currently housed in these other brain banks came from individuals who also had PTSD.

For example, there are now brain banks for depressive disorder. Depression is the most frequent comorbid disorder associated with PTSD. It can be expected that some brains in the depression brain bank will come from individuals with comorbid PTSD. On the other hand, it can also be expected that the PTSD brain bank will house specimens from individuals with PTSD and comorbid depression. By comparing tissue abnormalities from: a) depression alone; b) PTSD alone; and c) comorbid depression and PTSD, it will be pos-

sible to tease out the unique contributions of depression and PTSD to observed brain abnormalities.

Therefore, through collaborative activities and brain bank networks, it will be possible to identify PTSD–specific alterations through comparison with normal brains as well as with brains from depressed, alcohol dependent, and so forth, individuals.

WHAT ABOUT DEVELOPMENTAL ISSUES?

This is a key question at both ends of the life span. Questions concerning the elderly are easier to address. Aging produces changes in the brain. Sometimes such changes reflect normal processes while at other times they reflect deterioration due to atherosclerotic or Alzheimer's–related alterations. As veterans or other traumatized individuals grow older, it is important to understand the impact of traumatic stress on normal aging and on brains simultaneously undergoing progressive dementia.

With children, the major question is the impact of traumatic experiences on development. Are there critical periods in which traumatic exposure is especially deleterious to the developing brain? Perry (1994) has suggested that neonatal physical abuse may be especially disruptive before myelination has been completed. Does physical abuse affect brain development differently than sexual abuse or emotional abuse? These are some of the questions that would be important to investigate with postmortem tissue from traumatized children and adolescents.

WHAT SCIENTIFIC AND ETHICAL GUIDELINES SHOULD BE FOLLOWED REGARDING ACCESS TO THE BRAINS UTILIZED IN APPROVED RESEARCH?

We believe that a PTSD brain bank should be a national resource that is subjected to the most rigorous governmental and scientific oversight. As such, it should be supported by public funding and housed in the Department of Defense (DOD), Veterans Affairs (VA), or Health and Human Services. Its executive committee, consisting of eminent scientists, would be expected to adhere to the highest standards of scientific rigor and to ensure the strictest safeguards for protection of human subjects and privacy concerns. Independent oversight of the brain bank by an external data Safety Monitoring Board would insure compliance with such scientific and ethical standards.

It is expected that applicants who wish to utilize tissue housed in the brain bank would submit their proposals for peer review by a scientific committee convened for this purpose. Prioritization of submitted proposals would be conducted along time–tested peer review procedures. Access to brain tissue would be based on priority scores for scientific merit and availability of requested tissue (e.g., hippocampus, amygdala, etc.).

Hopefully, recurring sources for permanent support to house and manage the brain bank will become available. It is expected that independent investigators will need to develop their own support for their own research projects through extramural funding from National Institute of Health (NIH), VA, DoD, or private foundations.

WHO WOULD BENEFIT FROM A NATIONAL PTSD BRAIN BANK?

We believe that the public interest would be well served by such a facility. Given that exposure to traumatic stress is not uncommon, and that PTSD is a growing public health as well as public mental health problem (Schnurr & Green, 2004; Friedman, in press), questions about prevention, vulnerability/resilience and treatment are of paramount importance. We agree with Osuch et al. and Krystal & Duman (in this volume) that such questions cannot be answered adequately without access to high-quality tissue housed in a national PTSD brain bank.

In conclusion, we endorse the ongoing efforts of an advisory group consisting of experts from the Departments of Defense and Veterans Affairs. We support their efforts to create a stand–alone PTSD brain bank that would support scientific efforts to understand the etiology of PTSD and related disorders. The ultimate goal is, of course, the discovery of better preventive and therapeutic strategies with which to combat the development of posttraumatic medical and psychiatric disorders.

REFERENCES

Boscarino, J.A. (1997). Diseases among men 20 years after exposure to severe stress: Implications for clinical research and medical care. *Psychosomatic Medicine, 59,* 605–614.

Bremner, J.D., Innis, R.B., Ng, C.K., Chin, K., Staib, L.H., Salomon, R.M., Bronen, R.A., Duncan, J., Southwick, S.M., Krystal, J.H., Rich, D., Zubal, G., Day, H., Soufer, R., & Charney, D.S. (1997). PET measurement of central metabolic correlates of yohimbine administration in posttraumatic stress disorder. *Archives of General Psychiatry, 54,* 146–156.

Bremner, J.D., Innis, R.B., Southwick, S.M., Staib, L., Zoghbi, S., & Charney, D.S. (2000). Decreased benzodiazepine receptor binding in prefrontal cortex in combat related posttraumatic stress disorder. *American Journal of Psychiatry, 157,* 1120–1126.

Breslau, N., Davis, G.C., Andreski, P., & Peterson, E.L. (1991). Traumatic events and posttraumatic stress disorder in an urban population of young adults. *Archives of General Psychiatry, 48,* 216–222.

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., & Poulton, R. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5–HTT gene. *Science, 301,* 386–389.

Charney, D.S. (2004). Psychobiological mechanisms of resilience and vulnerability: Implications for the successful adaptation to extreme stress. *American Journal of Psychiatry, 161,* 195–216.

De Jong, J.T.V.M., Komproe, I.H., Van Ommeren, M., El Masri, M., Mesfin, A., Khaled, N., van de Put, W.A.M., & Somasundaram, D. (2001). Lifetime events and posttraumatic stress disorder in 4 postconflict settings. *Journal of the American Medical Association, 286, 555–562.*

Friedman, M.J. (in press). Towards a public mental health approach for survivors of terrorism. *Journal of Aggression, Maltreatment & Trauma.*

Galea, S., Ahern, J., Resnick, H.S., Kilpatrick, D.G., Bucuvalas, M.J., Gold, J., & Vlahov, D. (2002). Psychological sequelae of the September 11 terrorist attacks in New York City. *New England Journal of Medicine, 346*, 982–987.

Heim, C., Newport, D.J., Bonsall, R., Miller, A.H., & Nemeroff, C.B (2001). Altered pituitary–adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. *American Journal of Psychiatry, 158,* 575–581.

Kessler, R.C., Sonnega, A., Bromet, E., Hughes, M., & Nelson, C.B. (1995). Posttraumatic stress disorder in the National Comorbidity Survey. *Archives of General Psychiatry, 52,* 1048–1060.

Kulka, R.A., Schlenger, W.E., Fairbank, J.A., Hough, R.L., Jordan, B.K., Marmar, C.R., & Weiss, D.S. (1990). *Trauma and the Vietnam War Generation.* New York: Brunner/Mazel.

Norris, F., Friedman, M., Watson, P., Byrne, C., Diaz, E., & Kaniasty, K. (2002a). 60,000 disaster victims speak, Part I: An empirical review of the empirical literature, 1981–2001. *Psychiatry, 65*, 207–239.

Norris, F., Friedman, M., & Watson, P. (2002b). 60,000 disaster victims speak, Part II: Summary and implications of the disaster mental health research. *Psychiatry, 65* 240–260.

Perry, B.D. (1994). Neurobiological sequelae of childhood trauma: PTSD in children. In M. M. Murburg (Ed.), *Catecholamine Function in*

Post-Traumatic Stress Disorder: Emerging Concepts (pp. 233–255). Washington, DC: APA Press.

Schnurr, P.P., & Green, B.L. (Eds.). (2004). *Trauma and Health: Physical Health Consequences of Exposure to Extreme Stress*. Washington, DC: American Psychological Association.

Schuster, M., Bradley, D., Stein, M., Jaycox, L.H., Collins, R.L., Marshall, G.N., Elliott, M.N., Zhou, A.J., Kanouse, D.E., Morrison, J.L., & Berry, S.H. (2001). A national survey of stress reactions after the September 11, 2001, terrorist attacks. *New England Journal of Medicine, 345,* 1507–1512.